#2

PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PCT/GB03/03098

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed [signature]

Dated 6 August 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
Rule 16)

THE PATENT OFFICE
A
23 JUL 2002
LONDON

The Patent Office

1/77

24JUL02 E735459-1 D02639
P01/7700 0.00 -0217068.6
The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Request for grant of a patent

See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

0217068.6

Your reference	T1587PV
Patent application number (The Patent Office will fill in this part)	23 JUL 2002 0217068.6
Full name, address and postcode of the or of each applicant (underline all surnames)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Patents ADP number (if you know it)	00597799001
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
Title of the invention	Therapeutic agents
Name of your agent (if you have one)	Mr. I. J. Hiscock
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR
Patents ADP number (if you know it)	06546683001

If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority Application number (if you know it)	Date of filing (day/month/year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	21
Claim(s)	0
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

11. I/We request the grant of a patent on the basis of this application.

Signature ~~Signature~~ Date 22 July, 2002

Mr. I. J. Hiscock

12. Name and daytime telephone number of person to contact in the United Kingdom — Mr. I. J. Hiscock — 01279 440175

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

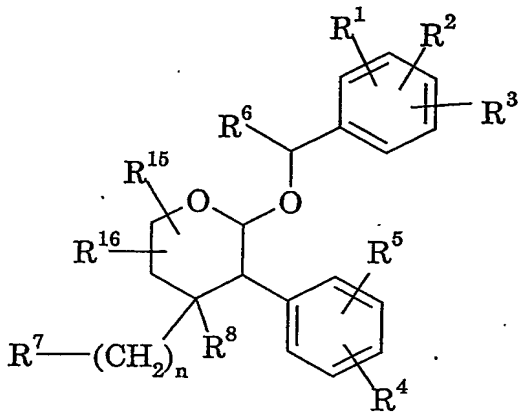
e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

THERAPEUTIC AGENTS

This invention relates to a class of tetrahydropyran compounds which are useful as tachykinin antagonists. More particularly, the compounds of the invention are useful as neurokinin 1 (NK-1) receptor antagonists.

The present invention provides compounds of the formula (I):



(I)

wherein

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

R^3 is hydrogen, halogen or fluoroC_{1-6}alkyl;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, hydroxy, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 is hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

R^6 represents hydrogen or a C_{1-4}alkyl group optionally substituted by a hydroxy group;

R^7 represents a 5- or 6-membered carbonyl or sulfonyl containing cyclic group comprising from 0 to 3 nitrogen ring atoms, from 0 to 1 oxygen ring atom and from 0 to 1 sulfur ring, wherein said ring is optionally substituted at any substitutable position by one or more substituents selected from =O, halogen, hydroxy, R^{11}, R^{12}, SR^f, SO_2R^g, COR^a, CO_2R^a, $CONR^9R^{10}$, -ZNR^9R^{10}, benzyl, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, fluoroC_{1-4}alkyl, chloroC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-7}cycloalkoxy, C_{3-7}cycloalkoxyC_{1-4}alkyl, C_{1-4}alkoxy, fluoroC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkoxy, aryl or arylC_{1-4}alkyl, wherein R^f is C_{1-4}alkyl or aralkyl or aryl and R^g is C_{1-4}alkyl, aryl, arylC_{1-4}alkyl or NR^9R^{10};

R^8 represents hydrogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl NR^9R^{10}, $CONR^9R^{10}$ or SO_2R^g;

R^9 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, fluoroC_{1-4}alkyl, C_{2-4}alkyl substituted by a C_{1-4}alkoxy or hydroxyl group, or R^9 is a five membered or six membered nitrogen-containing heteroaromatic ring as previously defined;

R^{10} is hydrogen or C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, fluoroC_{1-4}alkyl or C_{2-4}alkyl substituted by a C_{1-4}alkoxy or hydroxyl group;

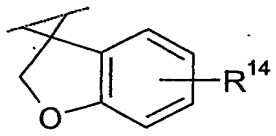
or R^9, R^{10} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy, COR^e, CO_2R^e, C_{1-4}alkyl optionally substituted by a C_{1-4}alkoxy or hydroxyl group, or C_{1-4}alkoxy optionally substituted by a C_{1-4}alkoxy or hydroxyl group, or a five membered or six membered nitrogen-containing heteroaromatic ring as previously defined, or said heteroaliphatic ring is substituted by a spiro-fused lactone ring, and said heteroaliphatic ring optionally containing a double bond, which heteroaliphatic ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^d moiety, where R^d is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^9, R^{10} and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or R^9, R^{10} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms to which is fused a benzene ring or a five membered or six membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S;

R^{11} and R^{12} each independently represent hydrogen, hydroxy, COR^e, CO_2R^e, C_{1-4}alkyl optionally substituted by a C_{1-4}alkoxy or hydroxyl group, or C_{1-4}alkoxy optionally substituted by a C_{1-4}alkoxy or hydroxyl group;

or, when they are attached to the same carbon atom, R^{11} and R^{12} may together represent =O, $=CHCO_2R^a$, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_k-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_k-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2C(CH_3)_2CH_2-$, $-OCH_2CH_2C(CH_3)_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, $-OCH_2CH_2C(O)CH_2-$, or a group of the formula



or, where they are attached to adjacent carbon atoms, R^{11} and R^{12} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{11} and R^{12} may together form a fused benzene ring;

or, R^{11} and R^{12} together form a C_{1-2}alkylene bridge across the pyrrolidine, piperidine, morpholine or piperazine ring to which they are attached;

R^{13} represents hydrogen, benzyl, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, $-SO_2C_{1-4}$alkyl or C_{2-4}alkyl substituted by a C_{1-4}alkoxy or hydroxyl group;

R^{14} represents hydrogen, halogen, hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or fluoroC_{1-4}alkyl;

R^{15} and R^{16} each independently represent hydrogen, halogen, C_{1-6}alkyl, CH_2OR^c, oxo, CO_2R^a or $CONR^aR^b$ where R^a and R^b are as previously defined and R^c represents hydrogen, C_{1-6}alkyl or phenyl;

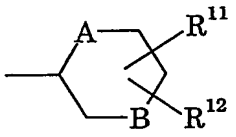
Z represents a bond, C_{1-6}alkylene or C_{3-6}cycloalkylene;

k is 1, 2 or 3;

m is 1 or 2; and

n is zero, 1 or 2;

with the proviso that when n is zero and R^8 is hydrogen, R^7 does not represent a C-linked nitrogen-containing ring of the formula



wherein

A represents NR^{13}, and B represents a bond, CH_2, NR^{13} or O, wherein one or both hydrogen atoms in said CH_2 moiety may be replaced with one or both of R^{11} and R^{12}, or alternatively, one of the hydrogen atoms in said CH_2 moiety together with a hydrogen atom from an adjacent carbon are replaced by a double bond; or A is O, and B is NR^{13}; and R^{11} and R^{12} together represent =O;

and pharmaceutically acceptable salts thereof.

A preferred class of compounds of formula (I) is that wherein R^1 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

Another preferred class of compounds of formula (I) is that wherein R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

Also preferred is the class of compounds of formula (I) wherein R^3 is hydrogen, fluorine, chlorine or CF_3.

A particularly preferred class of compounds of formula (I) is that wherein R^1 is fluorine, chlorine or CF_3.

Another particularly preferred class of compounds of formula (I) is that wherein R^2 is hydrogen, fluorine, chlorine or CF_3.

Also particularly preferred is the class of compounds of formula (I) wherein R^3 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^1 and R^2 are in the 3 and 5 positions of the phenyl ring.

More preferably R^1 is 3-fluoro or 3-CF_3.

More preferably R^2 is 5-fluoro or 5-CF_3.

More preferably R^3 is hydrogen.

Most preferably R^1 is 3-F or 3-CF_3, R^2 is 5-CF_3 and R^3 is hydrogen.

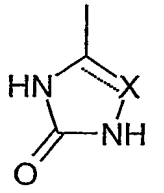
A further preferred class of compound of formula (I) is that wherein R^4 is hydrogen or fluorine, especially hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^5 is hydrogen, fluorine, chlorine or CF_3.

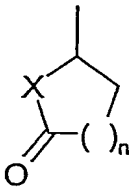
Preferably R^4 is hydrogen or 3-fluoro, especially hydrogen, and R^5 is hydrogen or 4-fluoro.

R^6 is preferably C_{1-4}alkyl optionally substituted by hydroxy. In particular, R^6 is preferably a methyl or hydroxymethyl group. Most especially, R^6 is a methyl group.

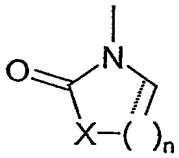
A further preferred class of compounds of formula (I) is that wherein R^7 is a cyclic group selected from the group consisting of:



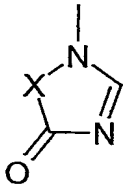
X is N, CH or CH_2 ,



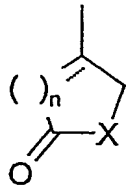
X is O or CH_2
n is 1 or 2 ,



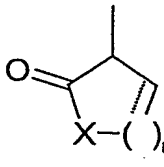
X is O, NH, CH_2 or NR^{13}
n is 1 or 2 ,



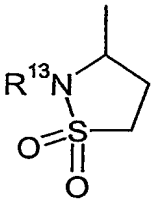
X is NH or CH_2 ,



X is O, NH, CH_2 or NR^{13}
n is 1 or 2 ,

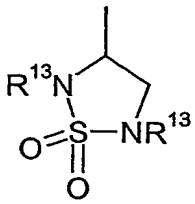


X is O, NH, CH_2 or NR^{13}
n is 1 or 2 ,

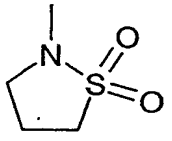


,

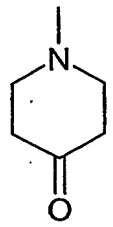
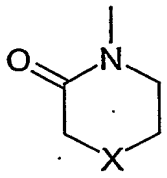
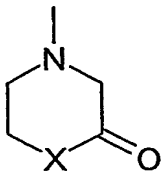
,



,

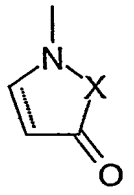
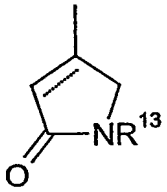
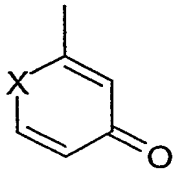


,


,

,

,

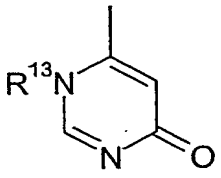
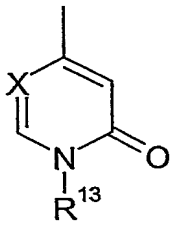
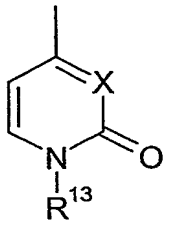
X is NR^{13} or CH_2

X is NR^{13} or CH_2


,

,

,

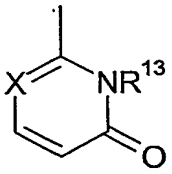
X is NR^{13} or CH_2

X is NR^{13}, O or SO_2


,

,

,

X is N or CH

X is N or CH


and

,

X is N or CH

wherein R^{13} is as previously defined, and further wherein any of said cyclic groups is optionally substituted by one or more (preferably one or two) groups as previously defined.

Another preferred class of compound of formula (I) is that wherein R^8 is hydrogen or methyl, and especially hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^{12} is hydrogen, hydroxy, C_{1-2}alkyl substituted by hydroxy, C_{1-4}alkoxy (especially methoxy) or CO_2R^e (where R^e is hydrogen, methyl ethyl or benzyl).

A further preferred class of compounds of formula (I) is that wherein R^{12} is hydrogen or C_{1-4}alkyl (especially methyl).

Where R^{11} and R^{12} are attached to the same carbon atom they may, in particular, together represent $-C(O)OCH_2CH_2-$.

In a further preferred class of compounds of formula (I), R^{13} preferably represents hydrogen, methyl or ethyl.

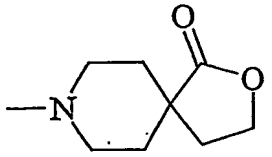
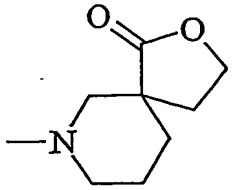
Another preferred class of compound of formula (I) is that wherein one of R^{15} and R^{16} is hydrogen, and especially wherein R^{15} and R^{16} are both hydrogen atoms.

A further preferred class of compound of formula (I) is that wherein n is zero or 1, and especially wherein n is zero.

In the definition of the group $-NR^9R^{10}$, R^9 may aptly be a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, R^{10} may aptly be a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, or R^9 and R^{10} may be linked so that, together with the nitrogen atom to which they are attached, they form an azetidinyl, pyrrolidinyl, piperidinyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxy or C_{1-2}alkoxy group. Particularly preferred heteroaliphatic rings formed by $-NR^9R^{10}$ are azetidine, pyrolidine, piperidine, morpholine, piperazine and N-methylpiperazine, and especially piperidine.

Where the group NR^9R^{10} represents a heteroaliphatic ring of 4 to 7 ring atoms substituted by two groups, the first substituent, where present, is preferably selected from hydroxy, CO_2R^e (where R^e is hydrogen, methyl, ethyl or benzyl), or C_{1-2}alkyl substituted by hydroxy. Where present, the second substituent is preferably a methyl group. Where two substituents are present, said substituents are preferably attached to the same carbon atom of the heteroaliphatic ring.

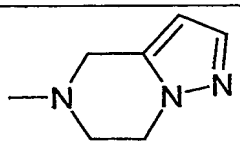
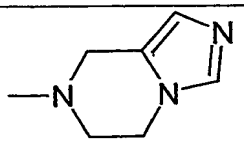
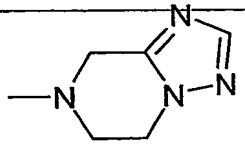
Where the group NR^9R^{10} represents a heteroaliphatic ring of 4 to 7 ring atoms substituted by a spiro-fused lactone ring, particularly preferred examples are:

 and 

Where the group NR^9R^{10} represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR^9R^{10} represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.3.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

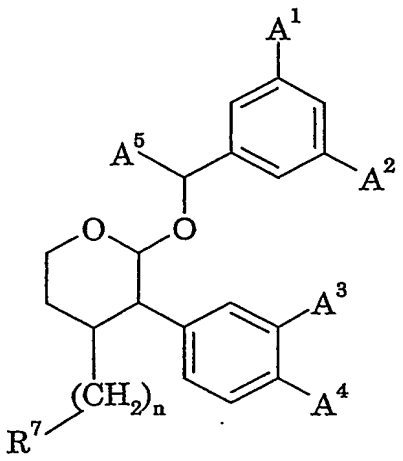
Where the group NR^9R^{10} represents a heteroaliphatic ring of 4 to 7 ring atoms to which is fused a benzene ring or a five membered or six membered nitrogen-containing heteroaromatic ring ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S, said heteroaromatic ring is preferably a five-membered ring, in particular a pyrrole, imidazole or triazole ring, a nitrogen atom of which is preferably included in the heteroaliphatic ring. Suitable examples of such fused ring systems include

 ,  and 

Particularly suitable moieties NR^9R^{10} include those wherein NR^9R^{10} is amino, methylamino, dimethylamino, diethylamino, azetidino, pyrrolidino, piperidino, morpholino and piperazino.

Favourably Z is a bond or contains 1 to 4 carbon atoms and most favourably 1 to 2 carbon atoms. A particularly favourable group Z is $-CH_2-$. The group $-ZNR^9R^{10}$, as a substituent on a heteroaromatic ring, is preferably $CH_2N(CH_3)_2$.

One favoured group of compounds of the present invention are of the formula (Ia) and pharmaceutically acceptable salts thereof:



(Ia)

wherein

A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

A^4 is fluorine or hydrogen;

A^5 is methyl; and

R^7 and n are as defined in relation to formula (I).

When any variable occurs more than one time in formula (I) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

As used herein, the terms "fluoroC_{1-6}alkyl" and fluoroC_{1-6}alkoxy" means a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by fluorine atoms. Similarly, the term "fluoroC_{1-4}alkyl" means a C_{1-4}alkyl group in which one or more (in particular 1 to 3) hydrogen

atoms have been replaced by fluorine atoms. Particularly preferred are fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3, OCF_3 and OCH_2CF_3.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

Similarly cycloalkoxy groups referred to herein may represent, for example, cyclopropoxy or cyclobutoxy.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

As used herein, the term "aryl" as a group or part of a group means an aromatic radical such as phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl or naphthyl group may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said phenyl, biphenyl or naphthyl group is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluormethoxy or vinyl.

Reference herein to "an optionally substituted five or six-membered ~~nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional~~ heteroatoms selected from N, O and S", is preferably reference to a heteroaromatic ring is selected from pyrrole, pyridine, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyrazine, pyrimidine, pyridazine, triazole, oxadiazole, thiadiazole, triazine, and tetrazole.

Suitable 5- or 6-membered cyclic ethers include optionally substituted tetrahydropyran and tetrahydrofuran rings.

When used herein the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred, unless otherwise stated.

In a further aspect of the present invention, the compounds of formula (I) may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

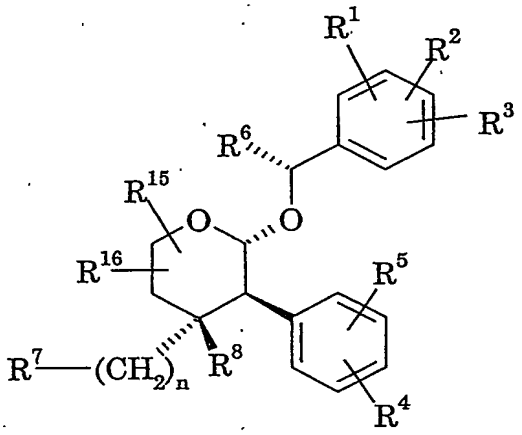
A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as

chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

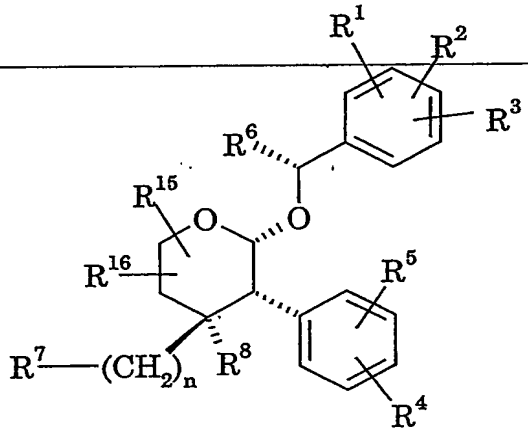
The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I) and (Ia) will have the stereochemistry of the 3-, 4- and 5-positions as shown in formulae (Ib) and (Ic)



(Ib)



(Ic)

It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless otherwise stated, apply to the generic formula for compounds of the present invention as well as to the preferred classes of compound represented by formula (Ia), formula (Ib) and formula (Ic).

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred.

A more detailed description of pharmaceutical compositions that are suitable for the formulation of compounds of the present invention is disclosed in US patent No. 6,071,927, the content of which is incorporated herein by reference (see in particular, column 8, line 50 to column 10, line 4).

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. A comprehensive listing of clinical conditions, uses and methods of treatment for which the compounds of the present invention will be useful is disclosed in US patent No. 6,071,927, the content of which is incorporated herein by reference (see, in particular, column 10, line 14 to column 22, line 18).

In particular, the compounds of the present invention are useful in the treatment of a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; and anxiety disorders, such as panic

disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders.

The compounds of the present invention are also particularly useful in the treatment of nociception and pain. Diseases and conditions in which pain predominates, include soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, migraine, episiotomy pain, and burns.

The compounds of the present invention are also particularly useful in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; in the treatment of inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; and in the treatment of allergic disorders such as eczema and rhinitis.

The compounds of the present invention are also particularly useful in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as ulcerative colitis, Crohn's disease and irritable bowel syndrome.

The compounds of the present invention are also particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents, including those routinely used in cancer chemotherapy; by radiation including radiation therapy such as in the treatment of cancer; and in the treatment of post-operative nausea and vomiting.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

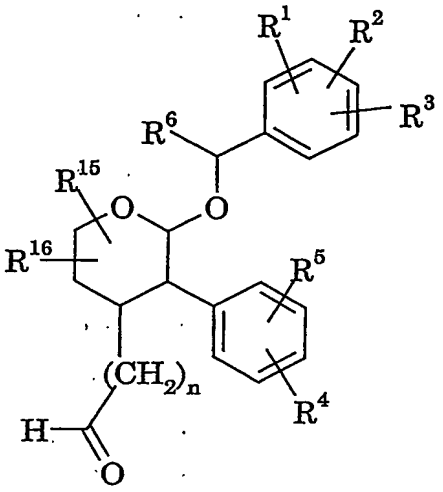
In the treatment of emesis, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of psychiatric disorders, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

As used herein, the term "treatment" includes prophylactic use to prevent the occurrence or recurrence of any of the aforementioned conditions.

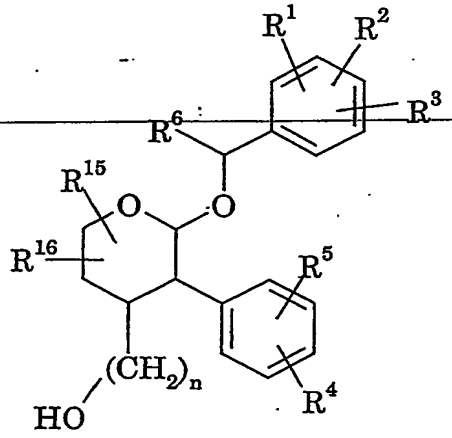
According to a general process (A), compounds of formula (I), in which R^7 is an N-linked cyclic group, may be prepared by the reaction of a compound of formula (II)



(II) (n = zero or 1)

with an amine of the formula HNR^9R^{10} in the presence of a reducing agent, for example, sodium triacetoxyborohydride or sodium cyanoborohydride. The reaction is conveniently effected in a suitable solvent such as a halogenated hydrocarbon, for example, 1,2-dichloroethane, conveniently at about room temperature.

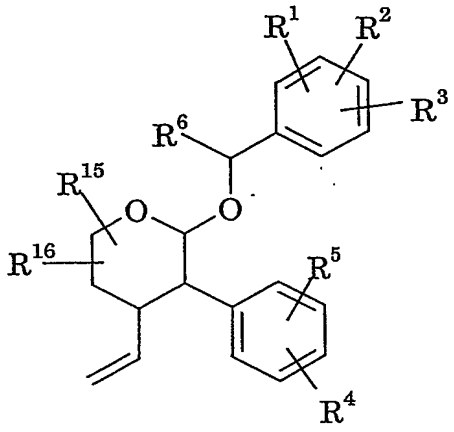
Compounds of formula (II) may be prepared by oxidation of a compound of formula (III)



(III) (n = 1 or 2)

The reaction is conveniently effected under conventional conditions suitable for the oxidation of a primary alcohol to an aldehyde without further oxidation to the carboxylic acid, for example, using Dess-Martin periodinane in a suitable solvent such as a halogenated hydrocarbon, for example, dichloromethane, conveniently at about room temperature.

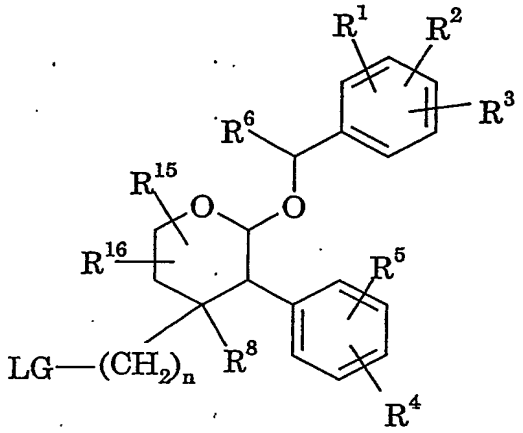
Compounds of formula (III) may be prepared by reaction of a compound of formula (V)



(V)

with ozone, followed by a reaction with a reducing agent such as sodium borohydride (n is 1), or by reaction with a reducing agent such as borane.tetrahydrofuran complex, followed by hydrogen peroxide in the presence of a base such as sodium hydroxide.

According to another general process (B), compounds of formula (I) may be prepared by the reaction of a compound of formula (VI)

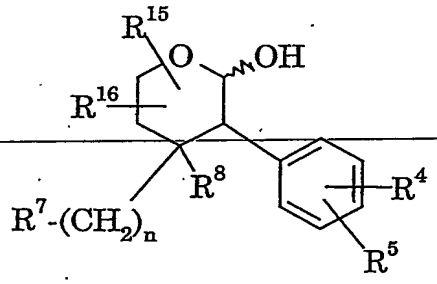


(VI)

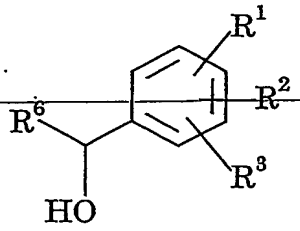
wherein LG is a suitable leaving group such as an alkyl- or arylsulfonyloxy group (e.g. mesylate or tosylate) or a halogen atom (e.g. bromine, chlorine or iodine); by reaction with an appropriate reactant to introduce a cyclic group as defined in relation to formula (I).

A particularly preferred compound of formula (VI) is that wherein the group LG is mesylate - i.e. the group $-OSO_2CH_3$.

According to another general process (C), compounds of formula (I) may be prepared by the reaction of a compound of formula (VII) with a compound of formula (VIII)



(VII)

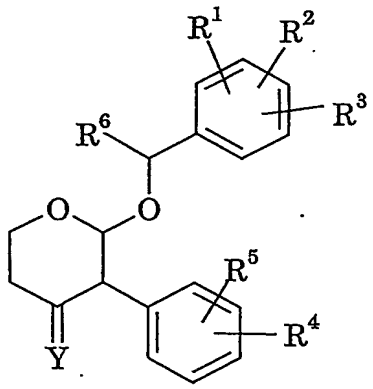


(VIII)

preferably in the presence of a resin catalyst such as Amberlyst™ 15, and 3 Angstrom molecular sieves.

The reaction is conveniently effected in a suitable solvent such as a halogenated hydrocarbon, for example, dichloromethane, conveniently at room temperature.

According to another general process (C), compounds of formula (I) wherein R^8 is other than hydrogen, may be prepared by the reaction of a compound of formula (XIV)

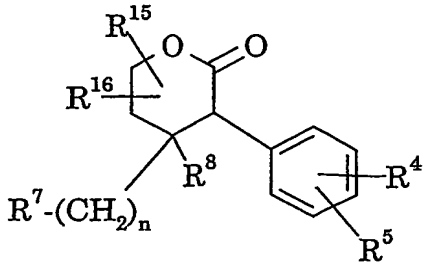


(XIV)

wherein Y is a suitable heteroatom or group such as an alkyl- or arylsulfinylimino group or an alkyl- or arylsulfonylimino group or an oxygen atom; by reaction with an appropriate nuclephilic reactant to introduce a R^7-$(CH_2)_n$ group as defined in relation to formula (I).

Compounds of formula (XIV) may be prepared by methods well known to one of ordinary skill in the art or by methods analogous to those described herein.

Compounds of formula (VII) may be prepared by the reduction of a compound of formula (IX)

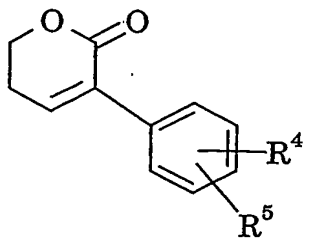


(VIII)

using conventional conditions such as sodium borohydride in the presence of a transition metal catalyst such as cerium chloride hexahydrate, in a solvent such

as alcohol, for example, ethanol; or using DiBAL in a solvent such as a halogenated hydrocarbon, for example, dichloromethane.

Compounds of formula (VIII) may be prepared from a compound of formula (X)



(X)

by reaction with a vinyl Grignard reagent such as $R^7(CH_2)_nMgBr$, preferably in the presence of copper(I)iodide, and a suitable solvent such as an ether, for example, tetrahydrofuran. This reaction is effected at reduced temperature, for example, below -40°C and preferably at -78°C.

Compounds of formula (VII) and (X) are either known compounds or may be prepared by methods analogous to those described herein.

Compounds of formula (VI) may be prepared by conventional methods from, for example, a corresponding compound of formula (I) in which R^7 is a hydroxyl group. Thus, for example, when LG is a mesylate group a corresponding compound of formula (I) in which R^7 is hydroxyl may be reacted with methanesulfonyl chloride in the presence of a base, such as triethylamine. The reaction is conveniently effected in a solvent such as a halogenated hydrocarbon, for example, dichloromethane.

It will be appreciated that the general methodology described above may be adapted, using methods that are readily apparent to one of ordinary skill in the art, in order to prepare further compounds of the present invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups

may be removed at a convenient subsequent stage using methods known from the art.

The compounds of this invention may be tested for their activity at the NK_1 receptor by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165.